Crossed Aldol Reaction Using Polymer-bound Lithium Amides

Atsushi Seki, Youichi Takizawa, Fusae Ishiwata, and Masatoshi Asami*
Department of Advanced Materials Chemistry, Graduate School of Engineering, Yokohama National University,
79-5 Tokiwadai, Hodogaya-ku, Yokohama 240-8501

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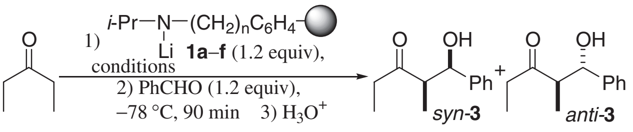
Polymer-bound lithium amides were used in an aldol reaction. The introduction of a spacer between the polymer backbone and the reactive site was important to enhance yields of the aldol products. The polymer-bound reagent was repeatedly used in the same reaction after the conversion to the lithium amide.

Lithium dialkylamides are widely employed in organic synthesis to form various carbanions by deprotonation of weakly acidic protons in the presence of a variety of functional groups. For example, the bases form regiodefined and geometrically controlled enolates from carbonyl compounds to afford crossed aldol adducts regio- and stereoselectively.[1]

On the other hand, much attention has been directed to polymer-bound reagents, since polymeric reagents are easily removed from the reaction mixture by filtration and can be recycled.[2] In spite of the importance of lithium dialkylamides in organic synthesis, few attempts to prepare and use polymer-bound lithium amide in organic synthesis were reported. To our knowledge, Cohen et al. first reported the preparation of a polymer-bound lithium dialkylamide in 1981,[3a] and Majewski et al. reported polymer-supported chiral lithium dialkylamides in enantioselective aldol reaction in 1999.[3b] Recently, we have reported polymer-bound achiral lithium dialkylamides as an in situ regenerator of chiral bases in a catalytic enantioselective rearrangement of *meso*-epoxides.[4] Here we wish to report preparation of cross-linked polymer-bound lithium dialkylamides with spacers between the base site and polymer backbone and their successful use in crossed aldol reaction.

Table 1. Aldol reaction of 3-pentanone with benzaldehyde using polymer-bound lithium amides **1a–f**



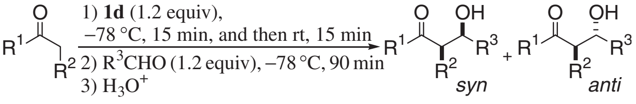
Entry	Li-amide	n	Conditions[a]	**3**/%[b]	*syn* : *anti*[c]
1	**1a**	1	A	65	68 : 32
2	**1a**	1	B	71	69 : 31
3	**1b**	2	B	78	71 : 29
4	**1c**	4	B	87	71 : 29
5	**1d**	5	A	82	69 : 31
6	**1d**	5	B	90	73 : 27
7	**1e**	6	B	89	72 : 28
8	**1f**	7	B	87	71 : 29
9	i-Pr_2NLi	—	A	88	62 : 38
10	i-Pr_2NLi	—	B	91	62 : 38

[a] Conditions A: The enolate was generated at −78 °C for 15 min. Conditions B: The enolate was generated at −78 °C for 15 min and then the resulting mixture was allowed to warm to room temp for 15 min.
[b] Isolated yield of aldol **3**. [c] Determined by ^{1}H-NMR analysis.

In the first place, we examined the aldol reaction between 3-pentanone and benzaldehyde using 1.2 equiv of polymer-bound lithium amide **1a**[4b] prepared from polymer-bound *N*-isopropyl-*p*-vinylbenzylamine (**2a**) and butyllithium. 1-Hydroxy-1-phenyl-2-methyl-3-pentanone (**3**) was obtained in 65% yield when the enolate was generated at −78 °C for 15 min from 3-pentanone and **1a** before the addition of benzaldehyde and stirring the reaction mixture for 90 min at −78 °C (Conditions A, Table 1, Entry 1). The yield was increased to 71% by warming up the reaction temperature gradually to room temp during the 15 min before the addition of benzaldehyde at −78 °C (Conditions B, Table 1, Entry 2). Then we examined introduction of spacers between the base site and the aromatic ring of the support to improve the yield of the reaction, because the modification of polymer-bound reagents with a spacer sometimes enhanced their performance.[5] The yield of **3** was increased gradually as the length of the spacer-chain became longer, and good yields comparable to that obtained by employing LDA were attained using polymer-bound lithium amides **1c–f**[4b,6–9] (Table 1, Entries 4–10).

As good results were obtained in the reaction of 3-pentanone and benzaldehyde, the reaction of 3-pentanone or cyclohexanone with several aldehydes was examined under Conditions B using **1d**. The results are summarized in Table 2. The corresponding aldol adducts were obtained in moderate to good yields. It is noted that a higher yield and/or syn/anti ratio were obtained in the reactions using the spacer-modified polymer-bound lithium amide **1d** compared to those obtained with LDA in some cases

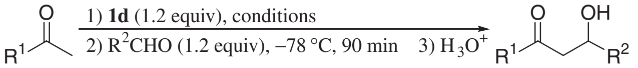
Table 2. Aldol reaction of 3-pentanone or cyclohexanone with aldehydes using **1d**



Entry	R^1, R^2	R^3	Yield/%[a,b]	*syn* : *anti*[b,c]
1	Et, Me	Ph	90 (91)	73 : 27 (62 : 38)
2		p-ClC_6H_4	88 (89)	74 : 26 (77 : 23)
3		o-$MeOC_6H_4$	84 (83)	65 : 35 (53 : 47)
4		*trans*-PhCH=CH	93 (83)	66 : 34 (60 : 40)
5		$Ph(CH_2)_2$	88 (90)	70 : 30 (71 : 29)
6		*n*-Pr	65 (70)	72 : 28 (70 : 30)
7	$-(CH_2)_4-$	Ph	82 (73)	27 : 73 (25 : 75)
8		$Ph(CH_2)_2$	56 (64)	30 : 70 (29 : 71)
9		*i*-Pr	59 (61)	3 : 97 (4 : 96)

[a] Isolated yield. [b] The figures in parentheses are the results obtained by using LDA in place of **1d**. [c] Determined by ^{1}H-NMR analysis.

Table 3. Aldol reaction of methyl ketones with aldehydes using **1d**



Entry	R^1	R^2	Conditions[a]	Yield/%[b]
1[c]	$Me(CH_2)_2$	Ph	B	67
2[c]			A	76
3			A	88 (83)[d]
4		$Ph(CH_2)_2$	A	93 (86)[d]
5		c-C_6H_{11}	A	82 (79)[d]
6		i-Pr	A	79 (73)[d]
7	$Me_2C{=}CH$	Ph	A	81
8			B	81 (84)[d]
9	Me	Ph	A	80 (85)[d]

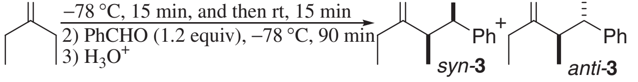
[a] Conditions A, B: see Table 1. [b] Isolated yield.
[c] Polymer **1a** was used in place of **1d**. [d] The figures in parentheses are the results obtained by using LDA in place of **1d**.

(Table 2, Entries 1, 3, 4, and 7).[10]

Next, the aldol reaction of 2-pentanone with benzaldehyde was carried out to examine the regioselectivity of the reaction using **1a** under Conditions B. The aldol adduct, 1-hydroxy-1-phenyl-3-hexanone, was obtained regioselectively in 67% yield (Table 3, Entry 1). In contrast to the results in the reaction of 3-pentanone, Conditions A gave a better yield (76%, Table 3, Entry 2). When the reaction was carried out under Conditions A using spacer-modified lithium amide **1d**, the yield was further improved to 88% (Table 3, Entry 3). A slightly higher yield compared to LDA was obtained in every case in the reactions of 2-pentanone with aldehydes using **1d** under Conditions A (Table 3, Entries 3–6). The enolate was generated regioselectively also from 4-methyl-3-penten-2-one with **1d**, and 1-hydroxy-5-methyl-1-phenyl-4-hexen-3-one was obtained in 81% (Table 3, Entries 7 and 8). A side reaction, e.g. 1,4-addition of lithium amide **1d** to the carbon-carbon double bond of 4-methyl-3-penten-2-one, did not take place. The reaction of the least hindered ketone, acetone, was not problematic, and the corresponding crossed aldol product, 4-hydroxy-4-phenyl-2-butanone was obtained in good yield by the reaction with benzaldehyde using **1d** (Table 3, Entry 9).

As the usefulness of spacer-modified polymer-bound lithium amide **1d** was realized, its recovery and repeated use were examined. After quenching the reaction, the used polymer-bound amine **2d** was recovered by filtration. The polymer-bound amine **2d** was successively washed with dichloromethane and water and dried under vacuum at 90 °C for 16 h. The polymer was then treated with butyllithium to regenerate **1d**. The regenerated **1d** was used in the same reaction between 3-pentanone and benzaldehyde. The yield and syn/anti ratio of **3** did not change significantly after the polymer **1d** was used five times (Table 4).

Table 4. Reuse of **1d**



Batch No.	1	2	3	4	5	6
Yield/%[a]	90	87	89	90	89	89
syn : *anti*[b]	73 : 27	70 : 30	69 : 31	70 : 30	71 : 29	69 : 31

[a] Isolated yield of aldol **3**. [b] Determined by ^{1}H-NMR analysis.

In conclusion, the cross-linked polymer-bound lithium amide **1d** with the appropriate spacer promotes crossed aldol reaction between ketones and aldehydes to afford aldols in up to 93% yield and is a reusable strong base. Furthermore, the effect of spacer to increase the reactivity of the polymer-bound lithium amide would be useful for the attachment of valuable lithium amides, e.g. chiral lithium amides, onto the polymer.

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References and Notes

1 C. H. Heathcock, in "Modern Synthetic Methods," ed. by R. Scheffold, Verlag Helvetica Chimica Acta, Basel (1992), Vol. 6, p 1; C. H. Heathcock, in "Comprehensive Organic Synthesis," ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 2, p 181.

2 For recent reviews; S. J. Shuttleworth, S. M. Allin, R. D. Wilson, and D. Nasturica, *Synthesis*, **2000**, 1035; S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, and S. J. Taylor, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3815; Y. R. de Miguel, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 4213; B. Clapham, T. S. Reger, and K. D. Janda, *Tetrahedron*, **57**, 4637 (2001); A. Kirschning, H. Monenschein, and R. Wittenberg, *Angew. Chem., Int. Ed. Engl.*, **40**, 650 (2001); C. A. McNamara, M. J. Dixon, and M. Bradley, *Chem. Rev.*, **102**, 3275 (2002).

3 a) B. J. Cohen, M. A. Kraus, and A. Patchornik, *J. Am. Chem. Soc.*, **103**, 7620 (1981). b) M. Majewski, A. Ulaczyk, and F. Wang, *Tetrahedron Lett.*, **40**, 8755 (1999).

4 a) M. Asami and A. Seki, *Chem. Lett.*, **2002**, 160. b) A. Seki and M. Asami, *Tetrahedron*, **58**, 4655 (2002).

5 For example; M. Tomoi and W. T. Ford, in "Syntheses and Separations Using Functional Polymers," ed. by D. C. Sherrington and P. Hodge, John Wiley & Sons, New York (1988), p 181; M. Tomoi, in "Handbook of Phase Transfer Catalysis," ed. by Y. Sasson and R. Neumann, Blackie Academic & Professional, London (1997), p 424.

6 *N*-Isopropyl-2-(vinylphenyl)ethylamine, a monomer for the preparation of **1b**, was prepared from divinylbenzene and isopropylamine in the presence of lithium isopropylamide; M. Maeda, Y. Nitadori, and T. Tsuruta, *Makromol. Chem.*, **181**, 2245 (1980).

7 Monomers for preparation of **1c–f** were prepared by the treatment of excess isopropylamine with ω-bromoalkylstyrenes, which were obtained according to the literature; M. Tomoi, E. Ogawa, Y. Hosokawa, and H. Kakiuchi, *J. Polym. Sci., Polym. Chem. Ed.*, **20**, 3015 (1982).

8 Selected data for isopropyl[5-(4-vinylphenyl)pentyl]amine, a monomer for polymer-bound amine **2d**: IR(neat): 3291, 3085, 2964, 2930, 2856, 1630, 1562, 1512, 1461, 1378, 1362, 842, and 730 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.04 (6H, d, $J = 6.3$ Hz), 1.26–1.41 (2H, m), 1.45–1.54 (2H, m), 1.56–1.68 (2H, m), 2.57 (2H, t, $J = 7.3$ Hz), 2.60 (2H, t, $J = 7.6$ Hz), 2.77 (1H, sept, $J = 6.3$ Hz), 5.18 (1H, dd, $J = 10.9$ Hz, 1.0 Hz), 5.70 (1H, dd, $J = 17.5$ Hz, 1.0 Hz), 6.69 (1H, dd, $J = 17.8$ Hz, 10.9 Hz), and 7.12–7.34 (4H, m).

9 Selected data for polymer-bound amine **2d**: $-50 + 100$ mesh polymer-bound isopropyl[5-(4-vinylphenyl)pentyl]amine: IR(KBr) 3083, 3060, 2925, 1493, 1377, 836, 758, and 699 cm^{-1}; Anal. Calcd for $(C_8H_8)_{0.78}\cdot(C_{16}H_{25}N)_{0.2}\cdot(C_{10}H_{10})_{0.02}$: C, 88.99; H, 8.86; N, 2.15%. Found: C, 88.51; H, 9.05; N, 2.35%.

10 General experimental procedure using **1d**: To a suspension of $-50 + 100$ mesh polymer-bound isopropyl[5-(4-vinylphenyl)pentyl]amine (**2d**) (1.68 mmol/g, 0.78 g, 1.3 mmol) in THF (6 mL) was added a hexane solution of butyllithium (1.58 M, 0.76 mL, 1.2 mmol) at room temp and the reaction mixture was stirred for 0.5 h. Ketone (1.0 mmol) in THF (2 mL) was added dropwise to the reaction mixture at −78 °C and stirring was continued for 15 min. After the mixture was allowed to warm to room temp for 15 min, aldehyde (1.2 mmol) was added to the mixture at −78 °C. After keeping the temperature at −78 °C for 90 min, the reaction was quenched with phosphate buffer (pH 7). The resin was filtered off, washed with CH_2Cl_2 and H_2O, and dried in vacuo at 90 °C for 16 h. The organic filtrate was washed with brine and dried over anhyd Na_2SO_4. After removal of the solvents under reduced pressure, the crude product was purified by preparative TLC or silica-gel chromatography, giving the β-hydroxy ketone.